and one proton are transported across the membrane with glutamate and one K^+ ion is transported in the opposite direction, allows a gradient of glutamate to be maintained such that the extracellular concentration is up to a million times lower than the intracellular concentration. This is necessary because prolonged activation of glutamate receptors on the extracellular surface of nerve cells is toxic — and high concentrations of glutamate are already present within the cells[6].

A common theory invoked to explain flux coupling in glutamate and other transporters proposes a conformational transition that allows alternating access to the transporter by intracellular and extracellular substrates[9]. But how do transporters accomplish this in a manner that prevents substrates from simply diffusing through the transporter down their electrochemical gradients? To understand this, we need to elucidate the nature of the 'gating' machinery involved. The structure and molecular model discussed by Yernool *et al.*[2] go some way towards providing both explanations and testable predictions.

The authors solved the structure of a transporter, Glt_{Ph}, from the thermophilic archaeal species *Pyrococcus horikoshii*, and refined it to a resolution of 3.5 Å to reveal a wealth of interesting features. This protein shares more than 35% amino-acid sequence identity with human glutamate transporters, but an important caveat is that glutamate-transport activity has not yet been demonstrated for this archaeal transporter. This may relate to special temperature requirements, or to modulation by specific lipids as exhibited by some bacterial (and mammalian) glutamate transporters[6]. Nevertheless, signature sequences and elements of the three-dimensional structure of Glt_{Ph} are consistent with a large body of biochemical and biophysical data for mammalian glutamate transporters. Furthermore, an electron density consistent with a bound molecule of glutamate, which was present during crystallization, is found nestled between the re-entrant hairpin loops, where it is poised to interact with key amino acids in TMDs 7 and 8 (ref. 2).

The folding pattern seen in the structure is distinct from that seen for the other transporters, pumps and channels that have been crystallized so far. The existence of the re-entrant loops is now confirmed. A provocative and attractive model put forward by Yernool *et al.* is that these hairpin loops, HP1 and HP2, serve as the gates controlling intracellular and extracellular access, respectively. This mechanism is quite distinct from the 'rocker-switch' type mechanism suggested by the MFS structures[7]. Coordinated movement of the loops could allow alternating access without an 'open channel' state. The state crystallized in the presence of glutamate is consistent with its being occluded, with the loops closed upon the substrate. Movements of these gates would be consistent with biochemical and fluorescence data that suggest that the protein's conformation changes in a state-dependent fashion when glutamate and ions bind[6,8,10].

Curiously, a chloride-channel activity is also observed in glutamate transporters, although chloride flux is not stoichiometrically coupled to that of glutamate[6]. Amino acids in the surrounding amino-terminal helices, especially helix 2, have been implicated in the function of this channel[11], but details of its location and mechanism of gating await further data.

Another interesting feature of the transporter is its trimeric structure[2], confirming previous experimental suggestions[6] of a multimeric nature for glutamate transporters. Yernool *et al.* have tentatively identified three binding sites for glutamate, one in each subunit, hinting that each subunit might function independently. So why is the transporter multimeric? That remains to be seen. The structure shows that three wedge-shaped subunits assemble to form a bowl-like structure, in which the basin faces the extracellular solution and the smaller base faces the cytoplasm (Fig. 1b). The deep, hydrophilic surface of the basin interior dips far into the plane of the membrane and may provide an aqueous 'waiting area' for transported solutes. But the role of this feature awaits more information, including the precise entry path for glutamate and ions into each subunit.

Even more crucial is the need for information about the conformational transitions that occur before and after ion and glutamate binding — transitions that are central to the alternating-access hypothesis. The new structure and model[2] are not the final word, but they suggest some promising experimental paths towards a satisfying explanation of how transporters work at the submolecular level. ■

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1. Bergles, D. E., Diamond, J. S. & Jahr, C. E. *Curr. Opin. Neurobiol.* **9,** 293–298 (1999).
2. Yernool, D., Boudker, O., Jin, Y. & Gouaux, E. *Nature* **431,** 811–818 (2004).
3. Stern, J. R., Eggleston, L. V., Hems, R. & Krebs, H. A. *Biochem. J.* **44,** 410–418 (1949).
4. Logan, W. J. & Snyder, S. H. *Nature* **234,** 297–299 (1971).
5. Kanner, B. I. & Sharon, I. *Biochemistry* **17,** 3949–3953 (1978).
6. Danbolt, N. C. *Prog. Neurobiol.* **65,** 1–105 (2001).
7. Locher, K. P., Bass, R. B. & Rees, D. C. *Science* **301,** 603–604 (2004).
8. Borre, L. & Kanner, B. I. *Biochim. Biophys. Acta* **1555,** 92–95 (2002).
9. Jardetzky, O. *Nature* **211,** 969–970 (1966).
10. Larsson, H. P., Tzingounis, A. V., Koch, H. P. & Kavanaugh, M. P. *Proc. Natl Acad. Sci. USA* **101,** 3951–3956 (2004).
11. Ryan, R. M., Mitrovic, A. D. & Vandenberg, R. J. *J. Biol. Chem.* **279,** 20742–20751 (2004).

100 YEARS AGO

As a constant reader of NATURE and of papers read before scientific societies, I have been struck by what seems to me an inaccurate use of language by English men of science which is rarely chargeable upon Americans — which is, at any rate, at variance with American usage. I will illustrate with the following examples:—One star is five light-years distant; another is twenty-five light-years distant. The English astronomer will say that the second is *five times farther away* than the first. A mass of aluminium weighs one pound; a mass of lead of equal size weighs something more than four pounds. The English physicist will say that the aluminium is *more than four times lighter* than the lead. Both expressions seem to me incorrect and unworthy of a man of science who endeavours to express himself accurately. In the one case he should say that one star is five times *as far away* as the other. In the other case the whole expression is vicious. Weight, heaviness, is an attribute of matter; lightness is absence, or deficiency, of weight. To say that one article is a certain number of times *lighter than* another is like saying of two vessels unequally exhausted of air that one is four times emptier than another. It is good English — is it not? — to say that one article is twice as heavy as another. If it is twice heavier, it is three times as heavy. I submit this criticism of an Anglicism as an offset to some one of many criticisms of Americanisms. E. S., Boston, U.S.A.

From *Nature* 13 October 1904.

50 YEARS AGO

On September 6, President Eisenhower announced that agreement had been reached between the United States and six other nations to establish an international agency which would foster the growth and spread of the new atomic technology for peaceful purposes. Atomic materials would be set aside for projects sponsored by the agency, and when arrangements were complete the United States would establish a reactor school to train representatives of friendly nations in the skills needed for their own atomic purposes… Mr Dulles, the American Secretary of State,… indicated that it was now proposed to create an international agency the initial membership of which included nations from all regions of the world… No nation would be excluded from participation in this venture.

From *Nature* 16 October 1954.